In line 4, replace " aid" with –an–; add --or isolated– after "ls lated"; and, add – r both– aft r "immunophilin".

REMARKS

Claims 1, and 4-8 are pending. All claims stand rejected. Applicant requests reconsideration of all rejections in the light of the amendments above and arguments below.

Specification

The examiner objects to the use of the superscript ® after the names SANDIMMUNE and CYCLOTRAC, and wishes the R to be encircled. These two superscripts have been removed altogether in order to place all marks and trade names in conformity with MPEP 608.01(v) which permits the use of all capitals or superscript Rs to denote marks and tradenames, and with the remainder of the specification that follows this practice. (See also examiner-suggested paragraph 6.20 in the MPEP).

Claim Rejections-35 USC 112

Claims 1, 4-8 have been rejected under 35 USC 112, second paragraph.

The examiner appears to be unclear as to the meaning of the term Kd in claim 4. This term has been an art-recognized expression for a binding constant for many decades and is common knowledge. The federal courts are in agreement that that which is well known in the art need not be described in a patent application. Nevertheless, to assist the examiner, the expression "binding constant" has been added to claim 4 as a modifier of the term Kd. This rejection of claim 4 should be withdrawn.

The examiner rejects claim 7 based on an argument that this claim recites a recombinant 8.4 kDa immunophilin, whereas the reference is said to be to the isolated 8.4 kDa immunophilin of claim 1. Applicant thanks the examiner for picking up on this possible ambiguity. Claim 7 has now been amended to clarify that the recombinant protein is related to the isolated protein insofar as the listed characteristics are concerned. This rejection should be withdrawn.

Claim 8 has been amended so as to remove the offending "said", and to recite that the kit can contain either the isolated or recombinant 8.4 kDa immunophilin, or both. This rejection should be withdrawn.

Claims 1 and 8 have been rejected on an assertion that the claims do not provide th me ts and bounds of pharmacologically active metab lites r

derivativ s. FK-506 and rapamycin are xtremely complex molecules of th class of macrocyclic lacton s. Rapamycin has an empirical formula of $C_{51}H_{79}N_1O_{13}$ of molwt 914.2. The empirical formula of FK-506 is $C_{44}H_{69}N_1O_{12}$ of molwt 822. The chemical name and actual structure of FK-506 and of rapamycine are shown in attached Exhibits 1 and 2, respectively. It is unreasonable to expect the applicant to know every possible derivative or metabolite of such a complex molecule that would be pharmacologically active, so as to be able to recite in the claim every conceivable modification of the chemical structure that is biologically active. As will be discussed in detail in the Written Description below, the present specification is replete with many references to specific metabolites and derivatives of the present macrocyclic lactones, inclusing those that are biologically active. This should be more than sufficient to show that applicant has described the invention in such terms as to make it clear to the public that he has the invention. It would be appropriate to withdraw these rejections.

Written Description

Claims 1, 4-8 are rejected under 35 USC 112, first paragraph, on an assertion that applicant has not provided sufficient examples of pharmacologically active derivatives and metabolites of FK-506 and rapamycin to support the generic recitation in these claims. The examiner concedes that the MPEP does not define what constitutes "sufficient examples", but then refers to In re Costelli, 872 F.2d at 1012, 10 USPQ2d at 1618 as suggesting that a sufficient number of examples to establish a genus should be greater than 2.

Applicant interjects here the notation that the examiner consistently appears to refer to the present immunosuppressive agents as "peptides" (see p. 5, second and third paragraphs, and p. 6 first paragraph of the Office Action), and his thinking appears to revolve about derivatives of "peptides". There is also reason to suspect from the examiner's writings on pp 5 and 6 of the Office Action that he may also be under the impression that applicant is claiming derivatives of the immunophilin protein. By the time he reaches this point in applicant's argument, one hopes that the examiner will understand that FK-506 and rapamycin are completely unrelated to peptides, and that applicant's references to metabolites and derivatives are in connection with the drugs, and not the 8.4 kDa immunophilin.

Returning to applicant's argument, the examiner's attention is directed to specification pages 2 and 12. On p. 2, lines 7-18 and lines 22-24 , there are described sixteen (16) known metabolites of rapamycin; of these, seven (7) are specifically identified as being biologically/pharmacologically active.

On p. 2, lines 21-23, immunosuppressant derivatives of rapamycin are identified.

On p. 12, lines 10-14, a pharmac logically active metabolite of FK-506 and five (5) pharmacologically active d rivatives of rapamycin are identified.

Applicant submits that he has far exceeded the standards of In re Castelli, cited by the examiner, as to the number of examples sufficient to establish a genus. Applicant thus has demonstrated with examples that "pharmacologically active" is a generic property that can itself define the metabolites and derivatives of the drugs that can specifically bind to the claimed 8.4 kDa immunophilins for assay purposes.

It would be appropriate for the examiner to withdraw all of these rejections.

Double Patenting

Claims 1, 4-8 are rejected under the doctrine of obviousness-type double patenting over claims 1-10 of applicant's own US Patent 6,410,340, issued 06/25/2002, maturing from USSN 09/643,723.

The examiner is respectfully reminded of the strictures of 35 USC §121. The third sentence of 35 USC §121 prohibits the examiner's use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 USC §121 prohibition applies only where the Office has made a requirement for restriction.

The examiner is informed that, in the US patent cited by the examiner for these rejections, a restriction requirement was made by the Office during the prosecution phase. Applicant elected the method of use claims (which became USPN 6,410,340), and canceled the composition claims. These composition claims became the subject of the present divisional application which was filed 02/13/2002, prior to the 06/25/2002 issuance date of the method patent. The examiner's attention is drawn to the first sentence of the present specification where the etiology of the present divisional application is recited. It should also be noted that both the present invention and the issued claims are under common ownership, namely, the Children's National Medical Center, Washington, DC.

For these reasons, examiner's rejections based on obviousness-type double patenting are inappropriate, and should be withdrawn.

With regard to kit claim 8, it has been amended to recite the recombinant 8.4 kDa immunophilin, which distinguishes this claim over claim 9 in the parent patent.

Conclusions

Applicant submits that he has overcome all claim rejections and objections, and that it would be appropriate to pass these claims to issuance.

Respectfully submitted,

Date 12/4/03

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Attorney for Applicant
Reg. No. 33,649

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T 202 363 3338
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CYCLOCORT® (amcinonide) Topical Cream 0.1% (1 mg/g) with AQUATAIN™ hydrophilic base

NDC 0469-7054-15 15 gram Tube	Product Code 705415
NDC 0469-7054-30 30 gram Tube	Product Code 705430
NDC 0469-7054-60 60 gram Tube	Product Code 705460

CYCLOCORT® (amcinonide) Topical Ointment 0.1% (1 mg/g)

NDC 0469-7115-15 15 gram Tube	Product Code 711515
NDC 0469-7115-30 30 gram Tube	Product Code 711530
NDC 0469-7115-60 60 gram Tube	Product Code 711560

Store at controlled room temperature 15°–30°C (59°–86°F). DO NOT FREEZE.

Manufactured for Fujisawa USA, Inc., Deerfield, IL 60015 by
Lederle Laboratories Division,
American Cyanamid Company,
Pearl River, NY 10965
CI 4432–1 Issued November 20, 1996

ELASE® OINTMENT ℞

[ē 'lāse]
(Fibrinolysin and Desoxyribonuclease, Combined, [Bovine] Ointment)

DESCRIPTION

Elase Ointment is a combination of two lytic enzymes, fibrinolysin and desoxyribonuclease, supplied in an ointment base of liquid petrolatum and polyethylene. The fibrinolysin component is derived from bovine plasma[1,2] and the desoxyribonuclease is isolated in a purified form from bovine pancreas. The fibrinolysin used in the combination is activated by chloroform.

HOW SUPPLIED

N0469-7004-30 Elase Ointment, 30-gram
The 30-gram tube contains 30 units of fibrinolysin and 20,000 units of desoxyribonuclease in a special ointment base of liquid petrolatum and polyethylene.
N0469-7004-10 Elase Ointment, 10-gram
The 10-gram tube contains 10 units of fibrinolysin and 6,666 units of desoxyribonuclease in a special ointment base of liquid petrolatum and polyethylene.
This product also contains sodium chloride and sucrose as incidental ingredients.
Storage: Store at no warmer than 30°C (86°F).
Caution—Federal law prohibits dispensing without prescription.

December 1994
Manufactured by
PARKE-DAVIS
Div of Warner-Lambert Co/Morris Plains, NJ 07950 USA
Distributed by
Fujisawa USA, Inc.
Deerfield, IL 60015 9011G023
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ELASE-CHLOROMYCETIN® OINTMENT ℞

(Fibrinolysin and Desoxyribonuclease, Combined, [Bovine] with Chloramphenicol Ointment)

DESCRIPTION

Elase-Chloromycetin Ointment contains two lytic enzymes, fibrinolysin and desoxyribonuclease, combined with chloramphenicol in an ointment base.
The fibrinolysin component is derived from bovine plasma,[1,2] and the desoxyribonuclease is isolated in a purified form from bovine pancreas. The fibrinolysin used in the combination is activated by chloroform.
Chloramphenicol is a broad-spectrum antibiotic originally isolated from *Streptomyces venezuelae*. It is therapeutically active against a wide variety of susceptible organisms, both gram-positive and gram-negative. Chemically, chloramphenicol may be identified as D(-)-*threo*-1-*p*-nitrophenyl-2-dichloroacetamido-1,3-propanediol.

HOW SUPPLIED

Elase-Chloromycetin (fibrinolysin-desoxyribonuclease-chloramphenicol) is supplied in 30-g and 10-g ointment tubes. The 10-g tubes have an elongated nozzle to facilitate the application to surface lesions.
N0469-7005-30 Elase-Chloromycetin Ointment, 30-gram. ... vine), 20,000 units* of desoxyribonuclease, and 0.3 g** chloramphenicol in a special ointment base of liquid petrolatum and polyethylene.
N0469-7005-10 Elase-Chloromycetin Ointment, 10-gram. The 10-g tubes contain 10 units (Loomis) of fibrinolysin (bovine), 6,666 units* of desoxyribonuclease, and 0.1 g** chloramphenicol in a special ointment base of liquid petrolatum and polyethylene.
The ointment contains sodium chloride and sucrose used in its manufacture.
Storage: Store at no warmer than 30°C (86°F).
Caution—Federal law prohibits dispensing without prescription.
* Modified Christensen method.[4]
** 10 mg chloramphenicol per gram, or 1%.

December 1994
Manufactured by
PARKE-DAVIS
Div of Warner-Lambert Co/
Morris Plains, NJ 07950 USA
Distributed by
Fujisawa USA, Inc.
Deerfield, IL 60015 9021G023
182

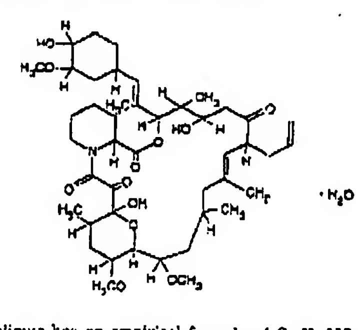
PROGRAF® ℞

tacrolimus capsules
tacrolimus injection (for intravenous infusion only)

> **WARNING**
> Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Prograf. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION

Prograf is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 1 mg or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 1 mg capsule shell contains gelatin and titanium dioxide, and the 5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide.
Prograf is also available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by intravenous infusion only. Each mL contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Prograf injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use.
Tacrolimus, previously known as FK506, is the active ingredient in Prograf. Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3S-[3R*[E(1S*,3S*,4S*)], 4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.
The chemical structure of tacrolimus is:



Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12} \cdot H_2O$ and a formula weight of 822.05. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

CLINICAL PHARMACOLOGY
Mechanism of Action
... dval of ... lant m... ... val and ... n, and ... n demo... to a gre... such as allograft reject... collagen-induc... arthri... graft ver...
Tacrolimus inhibits T-lymphocyte acti... exact mechanism of action is not know... dence suggests that tacrolimus binds... protein, FKBP-12. A complex of tacro... cium, calmodulin, and calcineurin is t... phosphatase activity of calcineurin i... may prevent the dephosphorylation and... clear factor of activated T-cells (NF-AT... nent thought to initiate gene transcripti... of lymphokines (such as interleukin-2,... The net result is the inhibition of T-ly... (i.e., immunosuppression).

Pharmacokinetics
Tacrolimus activity is primarily due to t... pharmacokinetic parameters (means ±... have been determined following intrav... (PO) administration in healthy volunte... and kidney transplant patients. (See ta...
[See table at bottom of next page]
Due to intersubject variability in tacr... netics, individualization of dosing regi... optimal therapy. (See DOSAGE AN... TION). Pharmacokinetic data indicat... concentrations rather than plasma con... the more appropriate sampling compa... tacrolimus pharmacokinetics.

Absorption
Absorption of tacrolimus from the gastr... ter oral administration is incomplete an... solute bioavailability of tacrolimus was... kidney transplant patients (N = 26), 22... transplant patients (N = 17), and 18 ± ... unteers (N = 16).
A single dose study conducted in 32 hea... tablished the bioequivalence of the 1 mg... Tacrolimus maximum blood concentratio... under the curve (AUC) appeared to incr... portional fashion in 18 fasted healthy vol... single oral dose of 3, 7 and 10 mg.
In 18 kidney transplant patients, tacrolim... trations from 3 to 30 ng/mL measured at... dose (C_{min}) correlated well with the AUC ... cient 0.93). In 24 liver transplant patients... tion range of 10 to 60 ng/mL, the correlati... 0.94.
Food Effects: The rate and extent of tacr... were greatest under fasted conditions. T... composition of food decreased both the r... tacrolimus absorption when administered t... unteers.
The effect was most pronounced with a hi... kcal, 46% fat): mean AUC and C_{max} were de... 77%, respectively; T_{max} was lengthened 5-f... hydrate meal (668 kcal, 85% carbohydrate... AUC and mean C_{max} by 28% and 65%, resp... In healthy volunteers (N = 16), the time ... affected tacrolimus bioavailability. When gi... following the meal, mean C_{max} was reduced... AUC was reduced 39%, relative to the ... When administered 1.5 hours following ... C_{max} was reduced 63%, and mean AUC ... relative to the fasted condition.
In 11 liver transplant patients, Prograf ... minutes after a high fat (400 kcal, 34% ... sulted in decreased AUC (27 ± 18%) and ... as compared to a fasted state.

Distribution
The plasma protein binding of tacrolimus ... 99% and is independent of concentratio... 5–50 ng/mL. Tacrolimus is bound mainly ... pha-1-acid glycoprotein, and has a high ... with erythrocytes. The distribution of ... whole blood and plasma depends on sev... hematocrit, temperature at the time of ... drug concentration, and plasma protein... U.S. study, the ratio of whole blood con... concentration averaged 35 (range 12 ...

Metabolism
Tacrolimus is extensively metabolized ... tion oxidase system, primarily the ... (CYP3A). A metabolic pathway leading ... possible metabolites has been propos... hydroxylation were identified as the ... biotransformation *in vitro*. The major ... In incubations with human liver ...

APPLICANT'S EXHIBIT Drug 2b/Tec

AIDSinfo **A Service of U.S. Department of Health and Human Services**

From the AIDSinfo Drugs Database

Technical View Non-Technical View

Generic Name:
Sirolimus [1]

Brand Name:
Rapamune [2]

CAS Name:
23,27-Epoxy-3H-pyrido(2,1-c)(1,4)oxaazacyclohentria
pentone, 9,10,12,13,14,21,22,23,24,25,26,27,32,33,3
dihydroxy-3-(3-(4-hydroxy-3-methoxycyclohexyl)-1-m
6,8,12,14,20,26-hexamethyl-, (3S-(3R*(S*
(1R*,3S*,4S*)),6S*,7E,9S*,10S*,12S*,14R*,15E,17E,
[3]

CAS Number:
53123-88-9 [4]

Therap utic Classification:

Immunosuppressant [5]

Physical Description:

Sirolimus occurs as a white to off-white powder. [6]

Solubility:

Sirolimus is freely soluble in benzyl alcohol, chlorofo
substantially insoluble in water. [7]

Molecular Formula:

C51-H79-N-O13 [8]

Molecular Weight:

914.17 [9]

Melting Point:

183-185 C [10]

Elemental Composition:

C 67.01%, H 8.71%, N 1.53%, O 22.75% [11]

Manufacturers:

Sirolimus
Wyeth - Ayerst Pharmaceuticals, PO Box 8299, F
(800) 934-5556

Rapamune
Wyeth - Ayerst Pharmaceuticals, PO Box 8299, F
(800) 934-5556

Other Name(s):

AY 22989 [12]